

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 April 2004 (15.04.2004)

PCT

(10) International Publication Number
WO 2004/031224 A2

(51) International Patent Classification⁷: **C07K 14/02**

(21) International Application Number:
PCT/US2003/031243

(22) International Filing Date: 1 October 2003 (01.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/415,018 1 October 2002 (01.10.2002) US

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 60/415,018 (CON)
Filed on 1 October 2002 (01.10.2002)

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(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT,
RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: HBV MUTATIONS ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO ADEFOVIR

(57) Abstract: Applicants have identified 5 mutants associated with hepatitis B virus resistance to adefovir, a nucleotide analogue antiviral drug widely employed in the therapy of hepatitis B. In accord with this invention, reverse transcriptase mutants rtN236T, rtA181V, rtA181T and their corresponding surface antigen mutants sL173F and sL172trunc are provided. The mutant proteins, antibodies thereto and nucleic acids encoding the mutants have diagnostic value in monitoring and adjusting patient therapy with adefovir and in the therapy of patients infected with the mutants.

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INTERNATIONAL SEARCH REPORT

Application No
CT/US 03/31243

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07K14/02 C12N9/12 C12N15/54 C12N15/36 C12N15/11 C12N15/62 C07K16/40 C07K16/08 A61K38/45 A61K38/16 A61K39/42					
According to International Patent Classification (IPC) or to both national classification and IPC					
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K C12N					
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched					
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EMBL, MEDLINE, BIOSIS, EMBASE, EPO-Internal, WPI Data, PAJ, CHEM ABS Data					
C. DOCUMENTS CONSIDERED TO BE RELEVANT					
Category *	Citation of document, with indication, where appropriate, of the relevant passages				Relevant to claim No.
X	DATABASE EMBL 'Online! "Mutant polymerase" retrieved from EBI Database accession no. Q9IN37 XP002277743 the whole document				1-5, 10-19,25
X	DATABASE EMBL 'Online! "Hepatitis B virus DNA polymerase variant-27" retrieved from EBI Database accession no. AAY71376 XP002277744 the whole document				1-5, 10-19,25
-/-					
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.					
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family					
Date of the actual completion of the international search			Date of mailing of the international search report		
26 April 2004			18/05/2004		
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016			Authorized officer Bladier, C		

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 03/31243

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL 'Online! "Polymerase" retrieved from EBI Database accession no. Q7THQ4 XP002277745 the whole document</p> <p>---</p>	<p>1-5, 10-19,25</p>
X	<p>DATABASE EMBL 'Online! "Type I mutant polymerase" retrieved from EBI Database accession no. Q918N7 XP002277747 the whole document</p> <p>---</p>	<p>1,5, 10-19,25</p>
X	<p>DATABASE EMBL 'Online! "Type IV mutant polymerase" retrieved from EBI Database accession no. Q918N8 XP002277746 the whole document</p> <p>---</p>	<p>1,5, 10-19,25</p>
P,X	<p>ANGUS P. ET AL.: "Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase." GASTROENTEROLOGY, vol. 125, no. 2, 2003, pages 292-297, XP002277740 cited in the application the whole document</p> <p>---</p>	<p>1-5, 10-25</p>
E	<p>WO 03/087351 A (MELBOURNE HEALTH, AUSTIN & REPATRIATION MEDICAL CENT, SOUTHERN HEALTH) 23 October 2003 (2003-10-23) Seq ID N°42, 43, 51 and 52.</p> <p>---</p>	<p>1-5, 10-25</p>
A	<p>DELANEY W.E. ET AL.: "RESISTANCE OF HEPATITIS B VIRUS TO ANTIVIRAL DRUGS: CURRENT ASPECTS AND DIRECTIONS FOR FUTURE INVESTIGATION" ANTIVIRAL CHEMISTRY & CHEMOTHERAPY, BLACKWELL SCIENTIFIC PUBL., LONDON, GB, vol. 12, no. 1, January 2001 (2001-01), pages 1-35, XP008005427 ISSN: 0956-3202 the whole document</p> <p>---</p>	

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INTERNATIONAL SEARCH REPORT

Int. Application No.
PCT/US 03/31243

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HUSSAIN M. ET AL.: "MUTATIONS IN THE HEPATITIS B VIRUS POLYMERASE GENE ASSOCIATED WITH ANTIVIRAL TREATMENT FOR HEPATITIS B"</p> <p>JOURNAL OF VIRAL HEPATITIS, BLACKWELL, OXFORD, GB, vol. 6, no. 3, May 1999 (1999-05), pages 183-194, XP000890068 ISSN: 1352-0504 the whole document</p> <p>---</p>	
T	<p>YANG H. ET AL: "Complete genotypic and phenotypic analysis of HBV mutations identified in HBeAg-negative chronic hepatitis B patients receiving 96 weeks of adefovir dipivoxil (ADV)."</p> <p>HEPATOLOGY, vol. 38, no. 4 suppl.1, October 2003 (2003-10), page 705A XP009029846 the whole document</p> <p>---</p>	
T	<p>BARTHOLOMEUSZ A. ET AL.: "Molecular modelling and functional studies of adefovir resistant mutations in the hepatitis B virus polymerase selected during therapy."</p> <p>HEPATOLOGY, vol. 38, no. 4, October 2003 (2003-10), page 273A XP009029890 the whole document</p> <p>-----</p>	

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 03/31243

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 18-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: **1-5, 10-25 (partially), 6-9 (completely)**
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5, 10-25 (partially), 6-9 (completely)

Present claim 1 relates to an extremely large number of possible nucleic acids. In fact, the claim contains so many nucleic acid options that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely for the HBV nucleic acids comprising sequences SEQ ID N°6, 8, 10, 12, 14, 16, 18, 20, 22, 24 (Table 3a) and for the HBV nucleotide sequences encoding amino acid sequences comprising GIHLTPDKT, GIHLTPTKT, GIHLTPNKT, GIHLTPHKT, PFLLVQFTS, PFLLTQFTS.

Present claims 6 and 8 relate to an extremely large number of possible Duck/Woodchuck hepatitis B virus reverse transcriptases or surface antigens. In fact, the claims contain so many options that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, no search has been carried out for these claims and also for claims 7 and 9 referring to these claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Int

Application No

PCT/US 03/31243

Patent document
cited in search reportPublication
datePatent family
member(s)Publication
date

WO 03087351

A

23-10-2003

WO

03087351 A1

23-10-2003

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